REMARKS

Claims 1-37 are pending. Claims 16-37 were withdrawn from consideration and claims 13-15 and 38-49 were previously cancelled.

Rejections Under 35 U.S.C. § 103(a)

Claims 1-12 are rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Tsien et al., (U.S. Patent No. 6, 469,154 (hereinafter "Tsien")) in view of McWherter et al., 1999 (Biochemistry, vol. 38, pp. 4564-4571 (hereinafter "McWherter")).

The claims are directed to methods for assembling a modulatable fusion molecule polypeptide, comprising generating a circular permutation of an insertion nucleic acid sequence, wherein the insertion nucleic acid sequence encodes a polypeptide that recognizes an input signal; and inserting the insertion sequence into an acceptor nucleic acid sequence, wherein the acceptor sequence encodes a polypeptide that produces an output signal provided the output signal is not fluorescence, wherein the fused insertion and acceptor sequences encode a modulatable fusion polypeptide.

The Examiner alleges that Tsien differs from the claimed invention in using a fluorescent output signal. However, the Examiner asserts that McWherter cures the deficiency. In particular, the Examiner alleges that McWherter teaches the use of myelopoietins (MPOs), which are engineered dual IL-3 receptor:colony-stimulating factor (G-CSF) receptor agonists, which were created by fusing circularly permuted G-CSF (cpG-CSG) sequences with sequences encoding an IL-3 receptor agonist moiety. The Examiner alleges that the substitution of one known element (G-CSF and IL-3 receptor agonists) for another (the flouresent protein and sensor protein taught by Tsien) would have been obvious at the time of invention because the substitution of the circularly permuted protein and sensor protein of McWherter for the circularly permuted protein and sensor of Tsien would have yeilded predictably results, namely IL-3 sensor protein control of circularly permuted G-CSF. Applicants respectfully disagree.

The test of obviousness requires that one compare the claimed "subject matter as a whole" with the prior art "to which said subject matter pertains" 35 U.S.C. § 103(a). To establish a *prima facie* case of obviousness, three criteria must be met. First, a suggestion or motivation to modify the reference or combine reference teachings must be present in the references or in the general knowledge present in the art. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations. M.P.E.P. 2143. The burden is on the Examiner to show that the references expressly or impliedly suggest all of the claim limitations. M.P.E.P. 2142. "There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons skilled in the art." *In re Rouffe*t, 149 F.3d 1350, 1357. In the absence of some teaching or suggestion to combine, no *prima facie* case of obviousness can be established, and the rejection is improper and must be withdrawn. *In re Fine*, 837 F.2d 1071, 1074. The references cited by the Examiner fail to provide the requisite teaching or suggestion to combine and fail to provide a reasonable expectation of success.

There is no suggestion or motivation to combine the sensor polypeptide of Tsien with the MPOs taught by McWherter. McWherter describes the generation of MPOs, which are fusion proteins consisting of an IL-3 receptor agonist fused to a G-CSF receptor agonist. However, the molecules described in McWherter are not modulatable fusion proteins, instead they are bi-functional molecules wherein the state of one ligand does not influence the state of the attached ligand. There is simply no motivation to add a sensor molecule to the MPOs of McWherter. Moreover, there is no reasonable likelihood of success. Tsien specifically teaches the fusion of a sensor polypeptide to a fluorescent protein. Nothing in Tsien teaches or suggests that fusing a sensor molecule to a non-fluorescent molecule would produce a functional modulateable fusion protein. Furthermore, both Tsien and McWherter fail to provide any teaching or guidance on how to select for a functional modulatable fusion protein switch and, therefore, they fail to teach all of the steps of the claimed method. Accordingly, the Examiner failed to make a primae facie case of obviousness and Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

For at least the foregoing reasons, each of the presently pending claims in this application is believed to be in condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue. Should any of the claims not be found to be in condition for allowance, the Examiner is requested to call Applicants' undersigned representative to discuss the application. Applicants thanks the Examiner in advance for this courtesy.

The Director is hereby authorized to charge or credit any deficiency in the fees filed, asserted to be filed, or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105. In view of the foregoing, Applicants request reconsideration and allowance of the pending claims.

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Respectfully submitted,

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